

Claims

What is claimed is:

1. A cell adhesion modulating agent that:
 - (a) comprises a claudin CAR sequence; and
 - (b) contains 3-16 amino acid residues linked by peptide bonds.

2. ^{B1} A modulating agent that:

(a) comprises at least five consecutive amino acid residues of a claudin CAR sequence having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.

3. A modulating agent that:

(a) comprises at least seven consecutive amino acid residues of a claudin CAR sequence having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.

4. A modulating agent that:

(a) comprises at least eight consecutive amino acid residues of a claudin CAR sequence having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

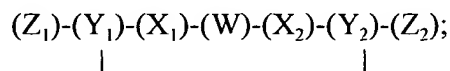
(b) contains no more than 50 consecutive amino acid residues present within the claudin.

5. A modulating agent according to any one of claims 2-4, wherein the agent is a peptide ranging in size from 3 to 50 amino acid residues.

6. A modulating agent according to any one of claims 1-4, wherein the agent is a peptide ranging in size from 4 to 16 amino acid residues.

7. A modulating agent according to any one of claims 1-4, wherein the CAR sequence is present within a cyclic peptide.

8. A modulating agent according to claim 7, wherein the cyclic peptide has the formula:



wherein W is a tetrapeptide selected from the group consisting of IYSY (SEQ ID NO:2), TSSY (SEQ ID NO:3), VTAF (SEQ ID NO:4), and VSAF (SEQ ID NO:5);

wherein X_1 , and X_2 are optional, and if present, are independently selected from the group consisting of amino acid residues and combinations thereof in which the residues are linked by peptide bonds, and wherein X_1 and X_2 independently range in size from 0 to 10 residues, such that the sum of residues contained within X_1 and X_2 ranges from 1 to 12;

wherein Y_1 and Y_2 are independently selected from the group consisting of amino acid residues, and wherein a covalent bond is formed between residues Y_1 and Y_2 ; and

wherein Z_1 and Z_2 are optional, and if present, are independently selected from the group consisting of amino acid residues and combinations thereof in which the residues are linked by peptide bonds.

9. A modulating agent according to claim 8, wherein Z_1 is not present and Y_1 comprises an N-acetyl group.

10. A modulating agent according to claim 8, wherein Z_2 is not present and Y_2 comprises a C-terminal amide group.

11. A modulating agent according to claim 8, wherein Y_1 and Y_2 are covalently linked via a disulfide bond.

12. A modulating agent according to claim 11, wherein Y_1 and Y_2 are each independently selected from the group consisting of penicillamine, β,β -tetramethylene cysteine, β,β -pentamethylene cysteine, β -mercaptopropionic acid, β,β -pentamethylene- β -mercaptopropionic acid, 2-mercaptobenzene, 2-mercaptoaniline, 2-mercaptoproline and derivatives thereof.

13. A modulating agent according to claim 11, wherein Y_1 and Y_2 are cysteine residues or derivatives thereof.

14. A modulating agent according to claim 8, wherein Y_1 and Y_2 are covalently linked via an amide bond.

15. A modulating agent according to claim 14, wherein the amide bond is formed between terminal functional groups.

16. A modulating agent according to claim 14, wherein the amide bond is formed between residue side-chains.

17. A modulating agent according to claim 14, wherein the amide bond is formed between one terminal functional group and one residue side chain.

18. A modulating agent according to claim 14, wherein:

(a) Y_1 is selected from the group consisting of lysine, ornithine, and derivatives thereof and Y_2 is selected from the group consisting of aspartate, glutamate and derivatives thereof; or

(b) Y_2 is selected from the group consisting of lysine, ornithine and derivatives thereof and Y_1 is selected from the group consisting of aspartate, glutamate and derivatives thereof.

19. A modulating agent according to claim 8, wherein Y_1 and Y_2 are covalently linked via a thioether bond.

20. A modulating agent according to claim 8, wherein Y_1 and Y_2 are each tryptophan or a derivative thereof, such that the covalent bond generates a $\delta_1\delta_1$ -dityryptophan, or a derivative thereof.

21. A polynucleotide encoding a modulating agent according to any one of claims 1-4.

21. 22. An expression vector comprising a polynucleotide according to claim

23. A host cell transformed or transfected with an expression vector according to claim 22.

24. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to a claudin CAR sequence and modulates a claudin-mediated function, wherein the claudin CAR sequence has the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine.

25. A modulating agent comprising a mimetic of a claudin CAR sequence that comprises at least three consecutive amino acid residues of a claudin CAR sequence having the formula

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine;

wherein the mimetic is capable of modulating a claudin-mediated function.

26. A modulating agent comprising a mimetic of a claudin CAR sequence that comprises at least five consecutive amino acid residues of a claudin CAR sequence having the formula

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine;

wherein the mimetic is capable of modulating a claudin-mediated function.

27. A modulating agent according to any one of claims 1-4 or 24-26 linked to a drug.

28. A modulating agent according to any one of claims 1-4 or 24-26 linked to a detectable marker.

29. A modulating agent according to any one of claims 1-4 or 24-26 linked to a targeting agent.

30. A modulating agent according to any one of claims 1-4 or 24-26 linked to a support material.

31. A modulating agent according to claim 30, wherein the support material is a polymeric matrix.

32. A modulating agent according to claim 30, wherein the support material is selected from the group consisting of plastic dishes, plastic tubes, sutures, membranes, ultra thin films, bioreactors and microparticles.

33. A cell adhesion modulating agent according to any one of claims 1-4 or 24-26, further comprising one or more of:

(a) a cell adhesion recognition sequence that is bound by an adhesion molecule other than a claudin, wherein the cell adhesion recognition sequence is separated from any claudin CAR sequence(s) by a linker; and/or

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(b) an antibody or antigen-binding fragment thereof that specifically binds to a cell adhesion recognition sequence bound by an adhesion molecule other than a claudin.

34. A cell adhesion modulating agent according to claim 33, wherein the adhesion molecule is selected from the group consisting of integrins, cadherins, occludin, N-CAM, fibronectin, laminin, and other extracellular matrix proteins.

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35. A pharmaceutical composition comprising a cell adhesion modulating agent according to any one of claims 1-4 or 24-26, in combination with a pharmaceutically acceptable carrier.

36. A composition according to claim 35, further comprising a drug.

37. A composition according to claim 35, wherein the cell adhesion modulating agent is present within a sustained-release formulation.

38. A composition according to claim 35, further comprising one or more of:

(a) a peptide comprising a cell adhesion recognition sequence that is bound by an adhesion molecule other than a claudin; and/or

(b) an antibody or antigen-binding fragment thereof that specifically binds to a cell adhesion recognition sequence bound by an adhesion molecule other than a claudin.

39. A composition according to claim 38, wherein the adhesion molecule is selected from the group consisting of integrins, cadherins, occludin, N-CAM, fibronectin, laminin and other extracellular matrix proteins.

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40. A modulating agent according to any one of claims 1-4, wherein the agent comprises one or more claudin-1 CAR sequences selected from the group consisting of: IYSY (SEQ ID NO:2), IYSYA (SEQ ID NO:27), IYSYAG (SEQ ID NO:28), KIYSY (SEQ

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ID NO:29), KIYSYA (SEQ ID NO:30), KIYSYAG (SEQ ID NO:31), WKIYSY (SEQ ID NO:32), WKIYSYA (SEQ ID NO:33) and WKIYSYAG (SEQ ID NO:34).

41. A modulating agent according to claim 40, wherein the agent comprises a linear peptide having the sequence N-Ac-WKIYSYAG-NH₂ (SEQ ID NO:34).

42. A modulating agent according to claim 40, wherein a claudin-1 CAR sequence is present within a cyclic peptide.

43. A modulating agent according to claim 42, wherein the cyclic peptide comprises a sequence selected from the group consisting of: CIYSYC (SEQ ID NO:59), CIYSYAC (SEQ ID NO:60), CIYSYAGC (SEQ ID NO:61), CKIYSYC (SEQ ID NO:62), CKIYSYAC (SEQ ID NO:63), CKIYSYAGC (SEQ ID NO:64), CWKIYSYC (SEQ ID NO:65), CWKIYSYAC (SEQ ID NO:66), CWKIYSYAGC (SEQ ID NO:67), KIYSYD (SEQ ID NO:68), KIYSYAD (SEQ ID NO:69), KIYSYAGD (SEQ ID NO:70), KKIYSYD (SEQ ID NO:71), KKIYSYAD (SEQ ID NO:72), KKIYSYAGD (SEQ ID NO:73), KWKIYSYD (SEQ ID NO:74), KWKIYSYAD (SEQ ID NO:75), KWKIYSYAGD (SEQ ID NO:76), KIYSYE (SEQ ID NO:77), KIYSYAE (SEQ ID NO:78), KIYSYAGE (SEQ ID NO:79), KKIYSYE (SEQ ID NO:80), KKIYSYAE (SEQ ID NO:81), KKIYSYAGE (SEQ ID NO:82), KWKIYSYE (SEQ ID NO:83), KWKIYSYAE (SEQ ID NO:84), KWKIYSYAGE (SEQ ID NO:85), DIYSYK (SEQ ID NO:86), DIYSYAK (SEQ ID NO:87), DIYSYAGK (SEQ ID NO:88), DKIYSYK (SEQ ID NO:89), DKIYSYAK (SEQ ID NO:90), DKIYSYAGK (SEQ ID NO:91), DWKIYSYK (SEQ ID NO:92), DWKIYSYAK (SEQ ID NO:93), DWKIYSYAGK (SEQ ID NO:94), EIYSYK (SEQ ID NO:95), EIYSYAK (SEQ ID NO:96), EIYSYAGK (SEQ ID NO:97), EKIYSYK (SEQ ID NO:98), EKIYSYAK (SEQ ID NO:99), EKIYSYAGK (SEQ ID NO:100), EWKIYSYK (SEQ ID NO:101), EWKIYSYAK (SEQ ID NO:102), EWKIYSYAGK (SEQ ID NO:103), IYSYA (SEQ ID NO:104), IYSYAG (SEQ ID NO:105), KIYSY (SEQ ID NO:106), KIYSYAG (SEQ ID NO:107), WKIYSY (SEQ ID NO:108), WKIYSYA (SEQ ID NO:109) and WKIYSYAG (SEQ ID NO:110).

44. A polynucleotide encoding a modulating agent according to claim 40.

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45. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the claudin-1 CAR sequence WKIYSYAG (SEQ ID NO:34).

46. A modulating agent according to any one of claims 1-4, wherein the agent comprises one or more claudin-2 CAR sequences selected from the group consisting of: TSSY (SEQ ID NO:3), TSSYV (SEQ ID NO:35), TSSYVG (SEQ ID NO:36), RTSSY (SEQ ID NO:37), RTSSYV (SEQ ID NO:38), RTSSYVG (SEQ ID NO:39), WRTSSY (SEQ ID NO:40), WRTSSYV (SEQ ID NO:41) and WRTSSYVG (SEQ ID NO:42).

47. A modulating agent according to claim 46, wherein the agent comprises a linear peptide having the sequence N-Ac-WRTSSYVG-NH₂ (SEQ ID NO:42).

48. A modulating agent according to claim 46, wherein a claudin-2 CAR sequence is present within a cyclic peptide.

49. A modulating agent according to claim 48, wherein the cyclic peptide comprises a sequence selected from the group consisting of: CTSSYC (SEQ ID NO:111), CTSSYVC (SEQ ID NO:112), CTSSYVGC (SEQ ID NO:113), CRTSSYC (SEQ ID NO:114), CRTSSYVC (SEQ ID NO:115), CRTSSYVGC (SEQ ID NO:116), CWRTSSYC (SEQ ID NO:117), CWRTSSYVC (SEQ ID NO:118), CWRTSSYVGC (SEQ ID NO:119), KTSSYD (SEQ ID NO:120), KTSSYVD (SEQ ID NO:121), KTSSYVGD (SEQ ID NO:122), KRTSSYD (SEQ ID NO:123), KRTSSYVD (SEQ ID NO:124), KRTSSYVGD (SEQ ID NO:125), KWRTSSYD (SEQ ID NO:126), KWRTSSYVD (SEQ ID NO:127), KWRTSSYVGD (SEQ ID NO:128), KTSSYE (SEQ ID NO:129), KTSSYVE (SEQ ID NO:130), KTSSYVGE (SEQ ID NO:131), KRTSSYE (SEQ ID NO:132), KRTSSYVE (SEQ ID NO:133), KRTSSYVGE (SEQ ID NO:134), KWRTSSYE (SEQ ID NO:135), KWRTSSYVE (SEQ ID NO:136), KWRTSSYVGE (SEQ ID NO:137), DTSSYK (SEQ ID

NO:138), DTSSYVK (SEQ ID NO:139), DTSSYVGK (SEQ ID NO:140), DRTSSYK (SEQ ID NO:141), DRTSSYVK (SEQ ID NO:142), DRTSSYVGK (SEQ ID NO:143), DWRTSSYK (SEQ ID NO:144), DWRTSSYVK (SEQ ID NO:145), DWRTSSYVGK (SEQ ID NO:146), ETSSYK (SEQ ID NO:147), ETSSYVK (SEQ ID NO:148), ETSSYVGK (SEQ ID NO:149), ERTSSYK (SEQ ID NO:150), ERTSSYVK (SEQ ID NO:151), ERTSSYVGK (SEQ ID NO:152), EWRTSSYK (SEQ ID NO:153), EWRTSSYVK (SEQ ID NO:154), EWRTSSYVGK (SEQ ID NO:155), TSSYV (SEQ ID NO:156), TSSYVG (SEQ ID NO:157), RTSSY (SEQ ID NO:158), RTSSYV (SEQ ID NO:159), RTSSYVG (SEQ ID NO:160), WRTSSY (SEQ ID NO:161), WRTSSYV (SEQ ID NO:162) and WRTSSYVG (SEQ ID NO:163).

50. A polynucleotide encoding a modulating agent according to claim 46.

51. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the claudin-2 CAR sequence WRTSSYVG (SEQ ID NO:42).

52. A modulating agent according to any one of claims 1-4, wherein the agent comprises one or more CPE-R CAR sequences selected from the group consisting of: VTAF (SEQ ID NO:4), VTAFI (SEQ ID NO:43), VTAFIG (SEQ ID NO:44), RVTAFF (SEQ ID NO:45), RVTAFFI (SEQ ID NO:46), RVTAFFIG (SEQ ID NO:47), WRVTAF (SEQ ID NO:48), WRVTAFI (SEQ ID NO:49) and WRVTAFIG (SEQ ID NO:50).

53. A modulating agent according to claim 52, wherein the agent comprises a linear peptide having the sequence N-Ac-WRVTAFIG-NH₂ (SEQ ID NO:50).

54. A modulating agent according to claim 52, wherein a CPE-R CAR sequence is present within a cyclic peptide.

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55. A modulating agent according to claim 54, wherein the cyclic peptide comprises a sequence selected from the group consisting of: CVTAFC (SEQ ID NO:164), CVTAFIC (SEQ ID NO:165), CVTAFIGC (SEQ ID NO:166), CRVTAFC (SEQ ID NO:167), CRVTAFIGC (SEQ ID NO:168), CRVTAFIGC (SEQ ID NO:169), CWRVTAFC (SEQ ID NO:170), CWRVTAFIGC (SEQ ID NO:171), CWRVTAFIGC (SEQ ID NO:172), KVTAFC (SEQ ID NO:173), KVTAFIGC (SEQ ID NO:174), KVTAFIGC (SEQ ID NO:175), KRVTAFC (SEQ ID NO:176), KRVTAFIGC (SEQ ID NO:177), KRVTAFIGC (SEQ ID NO:178), KWRVTAFC (SEQ ID NO:179), KWRVTAFIGC (SEQ ID NO:180), KWRVTAFIGC (SEQ ID NO:181), KVTAFIC (SEQ ID NO:182), KVTAFIE (SEQ ID NO:183), KVTAFIE (SEQ ID NO:184), KRVTAFC (SEQ ID NO:185), KRVTAFIGC (SEQ ID NO:186), KRVTAFIGC (SEQ ID NO:187), KWRVTAFC (SEQ ID NO:188), KWRVTAFIGC (SEQ ID NO:189), KWRVTAFIGC (SEQ ID NO:190), DVATFK (SEQ ID NO:191), DVTAFIK (SEQ ID NO:192), DVTAFIK (SEQ ID NO:193), DRVATFK (SEQ ID NO:194), DRVATFK (SEQ ID NO:195), DRVATFK (SEQ ID NO:196), DWRVATFK (SEQ ID NO:197), DWRVATFK (SEQ ID NO:198), DWRVATFK (SEQ ID NO:199), EVTAFK (SEQ ID NO:200), EVTAFIK (SEQ ID NO:201), EVTAFIK (SEQ ID NO:202), ERVATFK (SEQ ID NO:203), ERVATFK (SEQ ID NO:204), ERVATFK (SEQ ID NO:205), EWVATFK (SEQ ID NO:206), EWVATFK (SEQ ID NO:207), EWVATFK (SEQ ID NO:208), VTAFI (SEQ ID NO:209), VTAFI (SEQ ID NO:210), RVTAFC (SEQ ID NO:211), RVTAFC (SEQ ID NO:212), RVTAFC (SEQ ID NO:213), WRVTAFC (SEQ ID NO:214), WRVTAFC (SEQ ID NO:215) and WRVTAFC (SEQ ID NO:216).

56. A polynucleotide encoding a modulating agent according to claim 52.

57. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the CPE-R CAR sequence WRVTAFIG (SEQ ID NO:50).

58. A modulating agent according to any one of claims 1-4, wherein the agent comprises one or more RVP-1 CAR sequences selected from the group consisting of: VSAF (SEQ ID NO:5), VSAFI (SEQ ID NO:51), VSAFIG (SEQ ID NO:52), RVSAF (SEQ ID NO:53), RVSAFI (SEQ ID NO:54), RVSAFIG (SEQ ID NO:55), WRVSAF (SEQ ID NO:56), WRVSAFI (SEQ ID NO:57) and WRVSAFIG (SEQ ID NO:58).

59. A modulating agent according to claim 58, wherein the agent comprises a linear peptide having the sequence N-Ac-WRVSAFIG-NH₂ (SEQ ID NO:58).

60. A modulating agent according to claim 58, wherein a RVP-1 CAR sequence is present within a cyclic peptide.

61. A modulating agent according to claim 60, wherein the cyclic peptide comprises a sequence selected from the group consisting of: CVSAFC (SEQ ID NO:217), CVSAFIC (SEQ ID NO:218), CVSAFIGC (SEQ ID NO:219), CRVSAFC (SEQ ID NO:220), CRVSAFIC (SEQ ID NO:221), CRVSAFIGC (SEQ ID NO:222), CWRVSAFC (SEQ ID NO:223), CWRVSAFIC (SEQ ID NO:224), CWRVSAFIGC (SEQ ID NO:225), KVSAFD (SEQ ID NO:226), KVSAFID (SEQ ID NO:227), KVSAFIGD (SEQ ID NO:228), KRVSAFD (SEQ ID NO:229), KRVSAFID (SEQ ID NO:230), KRVSAFIGD (SEQ ID NO:231), KWRVSAFD (SEQ ID NO:232), KWRVSAFID (SEQ ID NO:233), KWRVSAFIGD (SEQ ID NO:234), KVSAFE (SEQ ID NO:235), KVSAFIE (SEQ ID NO:236), KVSAFIGE (SEQ ID NO:237), KRVSAFE (SEQ ID NO:238), KRVSAFIE (SEQ ID NO:239), KRVSAFIGE (SEQ ID NO:240), KWRVSAFE (SEQ ID NO:241), KWRVSAFIE (SEQ ID NO:242), KWRVSAFIGE (SEQ ID NO:243), DVSAFK (SEQ ID NO:244), DVSAFIK (SEQ ID NO:245), DVSAFIGK (SEQ ID NO:246), DRVSAFK (SEQ ID NO:247), DRVSAFIK (SEQ ID NO:248), DRVSAFIGK (SEQ ID NO:249), DWRVSAFK (SEQ ID NO:250), DWRVSAFIK (SEQ ID NO:251), DWRVSAFIGK (SEQ ID NO:252), EVSAFK (SEQ ID NO:253), EVSAFIK (SEQ ID NO:254), EVSAFIGK (SEQ ID NO:255), ERVSAFK (SEQ ID NO:256), ERVSAFIK (SEQ ID NO:257), ERVSAFIGK (SEQ ID NO:258), EWRVSAFK (SEQ ID NO:259), EWRVSAFIK (SEQ ID NO:260),

62. A polynucleotide encoding a modulating agent according to claim 58.

63. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the RVP-1 CAR sequence WRVSAFIG (SEQ ID NO:58).

63. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the RVP-1 CAR sequence WRVSAFIG (SEQ ID NO:58).